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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,550	10/04/2006	Hidetoshi Okabe	20080-00008	1617

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,550	OKABE, HIDETOSHI	
	Examiner	Art Unit	
	MEERA NATARAJAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments in the reply filed on 12/11/2007 are acknowledged and entered into the record.

2. Claims 1-20 are pending and will be examined on the merits.

Claim Rejections Maintained - 35 USC § 112

3. The rejection of Claims 1-20 under 35 USC 112 first paragraph regarding lack of enablement is maintained. The Applicant argues that a *prima facie* case of non-enablement has not been made because the rejection did not take into account the detection of the combination of receptor and ligand and their interaction in regards to usefulness of treatment. Applicant argues that the references cited in the 35 USC 112, first paragraph rejection only report HER2 expression in relation to prognosis of treatment and do not look at the interaction of HER2 and its ligand MUC4. In addition, Applicant's argue Price-Chiai et al. examine cell lines that have been transected to overexpress MUC4 and is not reflective of cells found in a human cancer cell that express human MUC4. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

4. The references provided show the unpredictability of determining patient outcome when administered an anticancer drug based on expression of specific genes. Although the references do not teach examining the expression of HER2 and MUC4 specifically, they do indicate the unpredictability of determining patient outcome based on the expression of any genes in general. Therefore, one of ordinary skill in the art would be required to perform undue experimentation to determine which combination of

any receptor and any ligand, as broadly claimed, would be associated with usefulness of an anticancer treatment. Applicant's only provide support for the combination of tumor-associated growth factor receptor HER2 and ligand MUC4, however there are several tumor-associated factor receptors that each have several ligands (i.e.: EGFR has various ligands, EGF, TGF-alpha, amphiregulin, heregulin, etc.) and therefore, undue experimentation would be required to enable the broad scope of the claims. Therefore, the rejection of the claims under 35 USC 112 first paragraph for lack of enablement is maintained for the reasons of record.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The method claimed does not include a correlating step. The method, as claimed, only recites the active steps of treatment with an anticancer drug and detection of HER2 and MUC4 expression in a tissue sample. The claimed method does not provide a correlating step to determine how expression levels correlate to drug treatment (i.e. expression or absence correlates with effectiveness).

8. Claim 1 is incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to

clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. Clarification is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price-Schiavi et al. ((Int. J. Cancer Vol. 99, p.783-791; 2002) in view of Witton et al. (J. of Pathology, Vol. 200, pp. 290-297, 2003) and Mandrand et al. (US Patent #5695936).

11. The claims are drawn to an examination method to evaluate usefulness of treatment with trastuzumab comprising detecting in a tissue sample ErbB2/HER-2 and MUC4 expression, wherein MUC4 interacts with ErbB2/HER2 to affect expression or function.

12. Price-Schiavi et al. teach the expression of Muc4 on MCF-7 breast cancer cells, which express c-erbB-2, form a complex with ErbB2 and provide a steric block to anti-ErbB2 antibody (trastuzumab) binding. The reduced binding of antibody would lead to a reduction in cytostatic effects and sensitization to other chemotherapies (see p. 789, right column, 2nd full paragraph). Therefore, this examination would predict that breast cancer patients that overexpress Muc4 and ErbB2 would *not* be responsive to trastuzumab therapy. Price-Schiavi et al. state "it is now common to screen breast tumors for a variety of molecular markers such as estrogen receptor and ErbB2 to determine the best course of treatment for a breast cancer patient. There is now increasing evidence that Muc4 is aberrantly expressed in a number of different cancers including breast cancers. Thus, along with other tumor markers, it may be useful to screen for Muc4 expression in determining the best course of treatment for a breast cancer patient" (see p. 789-790, right column, last paragraph). The method taught by Price-Schiavi et al. teach immunohistochemistry analysis of MUC4 in solid breast tumor samples obtained from patients with operable breast cancer (see "Material and Methods", p. 784, left column and Figure 1). Therefore, the method taught by Price-Schiavi et al. teach the active step of "detecting in an analyte sample the gene encoding a substance and/or the expressed product thereof that interacts with the receptor on the

surface of and/or within the cell membrane". Although the reference teaches expression of ErbB2/HER2 and MUC4 expression indicates a non-responsiveness to trastuzumab, which is not in accordance with the instant applications' disclosure, the reference teaches the active steps claimed and therefore teach the disclosed method. The reference does not teach detecting ErbB2/HER2 in an analyte sample or a kit. These deficiencies are made up for by Witton et al. and Mandrand et al.

13. Witton et al. teach expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. Expression of HER1-4 was determined by immunohistochemistry staining of tissue samples from 220 breast carcinomas. Witton et al. teach patients, whose tumors overexpressed HER1, 2, or 3 had reduced survival

14. Mandrand et al. teach a method for the detection of a nucleotide sequence with signal amplification. Mandrand et al. disclose "a kit for detecting a sequence of a nucleotide sequence of interest, with signal amplification, which kit comprises at least one nucleotide probe" (see Column 3, lines 34-51).

15. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to detect ErbB2/HER2 along with MUC4 expression in a breast cancer tissue samples. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Price-Schiavi et al. and Witton et al. because Price-Schiavi et al. disclose it is now common to screen breast tumors for a variety of molecular markers such as estrogen receptor and ErbB2 to determine the best course of treatment for a breast cancer patient and Witton et al. teach ErbB2/HER2 is overexpressed in breast cancer tissues

and correlates with poor survival. In addition, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to incorporate the reagents used to detect ErbB2/HER2 and MUC4 in a kit as taught by Mandrand et al. It is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Mandrand et al. to incorporate the reagents in a kit for reasons of convenience, efficiency, and economy.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in the reply filed 12/11/2007.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Thursday, 9:30AM-7:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN
/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643